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(54) Title: TREATMENT OF HYPERPROLIFERATIVE SKIN DISORDERS AND DISEASES

(57) Abstract: The invention relates to the use of one or more noble metals selected from silver, gold, platinum, and palladium but most preferably silver, in a nanocrystalline form, for the treatment of a hyperproliferative skin disorder or disease such as psoriasis. Among the noble metals, silver is preferred for such treatment. The nanocrystalline noble metal of choice may be used in the form of a nanocrystalline coating of one or more noble metals, a nanocrystalline powder of one or more noble metals, or a solution containing dissolved species from a nanocrystalline powder or coating of one or more noble metals.

Treatment of Hyperproliferative Skin Disorders and Diseases

FIELD OF THE INVENTION

The invention relates to the use of nanocrystalline noble metals for the treatment of hyperproliferative skin disorders and diseases such as psoriasis.

BACKGROUND OF THE INVENTION

In spite of many years of research on the treatment of hyperproliferative skin disorders and diseases such as psoriasis, there are still many patients suffering from such skin diseases for whom treatment regimes have been ineffective. Furthermore, many of the side effects from the medications currently prescribed for the treatment of psoriasis are problematic. Thus, there still remains a need for a safe and effective treatment for hyperproliferative skin disorders and diseases such as psoriasis and keratinization.

SUMMARY OF THE INVENTION

The inventors have discovered that nanocrystalline noble metals selected from one or more of silver, gold, platinum and palladium, are effective in the treatment of psoriasis. Preferably, these noble metals are formed with atomic disorder, such that ions, clusters, atoms or molecules of the metals are released on a sustainable basis.

The nanocrystalline forms of these noble metals may be used in any of the following formats:

i) nanocrystalline coatings of the noble metals on medical grade substrates, for example, dressings, fibers, and materials composed of for example polyethylene, high density polyethylene, polyvinylchloride, latex, silicone, cotton, rayon, polyester, nylon, cellulose, acetate, carboxymethylcellulose, alginate, chitin, chitosan and hydrofibres;

ii) gels, formulated with nanocrystalline powders of the noble metals with such materials as carboxymethylcellulose, alginate, chitin, chitosar and hydrofibres, together with such ingredients as pectin and viscosity enhancers;

iii) creams, lotions, pastes and ointments formulated with nanocrystalline powders of the noble metals, for example as emulsions or with drying emollients;

iv) liquids, formulated as solutions by dissolving nanocrystalline coatings or powders of the noble metals, for example as topical solutions, aerosols or mists;

v) powders, prepared as nanocrystalline powders of the noble metals, or as nanocrystalline coatings of the noble metals on biocompatible substrates in powder form, preferably on bioabsorbable and/or hygroscopic substrates such as:

Synthetic Bioabsorbable Polymers: for example polyesters/polyactones such as polymers of polyglycolic acid, glycolide, lactic acid, lactide, dioxanone, trimethylene carbonate etc., polyanhydrides, polyesteramides, polyortheoesters, polyphosphazenes, and copolymers of these and related polymers or monomers.

Naturally Derived Polymers:

Proteins: albumin, fibrin, collagen, elastin;

Polysaccharides: chitosan, alginates, hyaluronic acid; and

Biosynthetic Polyesters: 3-hydroxybutyrate polymers.

In the above formats, the nanocrystalline noble metals are formulated from nanocrystalline coatings or nanocrystalline powders of the nanocrystalline noble metals, or from solutions prepared by dissolving the nanocrystalline coatings or powders therein. The formulations include a therapeutically effective amount of the coatings or powders, and most preferably, the following amounts:

For coatings:	150 - 3000 nm thick coatings
For gels, creams and lotions:	0.01 - 5% by weight of the nanocrystalline noble metal powder
For liquids	0.001 - 1% by weight of the noble metal

Nanocrystalline coatings of the noble metals are most preferably deposited onto one or more layers of medical dressing materials which can be laminated with uncoated layers of medical dressing materials. The coatings can be prepared by known techniques for preparing nanocrystalline coatings, but are most preferably prepared by physical vapour deposition under conditions which create atomic disorder. The nanocrystalline coatings are most preferably prepared to create an interference colour so as to provide an indicator, as described in prior patent application WO 98/41095, published September 24, 1998, and naming inventors R. E. Burrell and R. J. Precht.

Nanocrystalline powders of the noble metals may be prepared as nanocrystalline coatings, preferably of the above thickness, on powdered substrates such as chitin, or may be prepared as nanocrystalline coatings on a substrate such as a silicon wafer, and then scraped off as a nanocrystalline powder. Alternatively, fine grained or nanocrystalline powders of the noble metals may be cold worked to impart atomic disorder, as disclosed in prior patent application WO 93/23092, published November 25, 1993, naming Burrell *et al.*, as inventors.

As used herein and in the claims, the terms and phrases set out below have the

meanings which follow.

"Metal" or "metals" includes one or more metals whether in the form of substantially pure metals, alloys or compounds such as oxides, nitrides, borides, sulphides, halides or hydrides.

"Noble metals" are silver, gold, platinum and palladium, or mixtures of such metals with same or other metals, with silver metal being the most preferred.

"Biocompatible" means non-toxic for the intended utility. Thus, for human utility, biocompatible means non-toxic to humans or human tissues.

"Sustained release" or "sustainable basis" are used to define release of atoms, molecules, ions or clusters of a noble metal that continues over time measured in hours or days, and thus distinguishes release of such metal species from the bulk metal, which release such species at a rate and concentration which is too low to be therapeutically effective, and from highly soluble salts of noble metals such as silver nitrate, which releases silver ions virtually instantly, but not continuously, in contact with an alcohol or electrolyte.

"Atomic disorder" includes high concentrations of: point defects in a crystal lattice, vacancies, line defects such as dislocations, interstitial atoms, amorphous regions, grain and sub grain boundaries and the like relative to its normal ordered crystalline state. Atomic disorder leads to irregularities in surface topography and inhomogeneities in the structure on a nanometer scale.

"Normal ordered crystalline state" means the crystallinity normally found in bulk metal materials, alloys or compounds formed as cast, wrought or plated metal products. Such materials contain only low concentrations of such atomic defects as vacancies, grain boundaries and dislocations.

"Diffusion", when used to describe conditions which limit diffusion in processes to create and retain atomic disorder, i.e. which freeze-in atomic disorder, means diffusion of atoms (adatom diffusion) and/or molecules on the surface or in the matrix of the material being formed.

"Alcohol or water-based electrolyte" is meant to include any alcohol, water, or water-based electrolyte that the anti-microbial materials of the present invention might contact in order to activate (i.e. cause the release of species of the anti-microbial metal) into same. The term is meant to include alcohols, water, gels, fluids, solvents, and tissues containing water, including body fluids (for example blood, urine or saliva), and body tissue (for example skin,

muscle or bone).

"Bioabsorbable" as used herein in association includes substrates which are useful in medical devices, that is which are biocompatible, and which are capable of bioabsorption in period of time ranging from hours to years, depending on the particular application.

"Bioabsorption" means the disappearance of materials from their initial application site in the body (human or mammalian) with or without degradation of the dispersed polymer molecules.

"Colour change" is meant to include changes of intensity of light under monochromatic light as well as changes of hue from white light containing more than one wavelength.

An "interference colour" is produced when light impinges on two or more partly reflective surfaces separated by a distance which bears the right relationship to the wavelength of the light to be removed by destructive interference.

"Partly reflective" when used to describe the base or top layer materials, means that the material has a surface which reflects a portion of incident light, but which also transmits a portion of the incident light. Reflection occurs when a ray of incoming light encounters a boundary or interface characterized by a change in refractive index between two media. For the top layer of the anti-microbial materials of this invention, that interface is with air. For the base layer, the interface is with the top layer. The reflectance of the base and top layers is balanced so as to generate an interference colour.

"Partly light transmissive" when used to describe a thin film of the top layer material means that the thin film is capable of transmitting at least a portion of incident visible light through the thin film.

"Detectable" when used to describe a colour change means an observable shift in the dominant wavelength of the reflected light, whether the change is detected by instrument, such as a spectrophotometer, or by the human eye. The dominant wavelength is the wavelength responsible for the colour being observed.

"Cold working" as used herein indicates that the material has been mechanically worked such as by milling, grinding, hammering, mortar and pestle or compressing, at temperatures lower than the recrystallization temperature of the material. This ensures that atomic disorder imparted through working is retained in the material.

"Therapeutically effective amount" is used herein to denote any amount of a

formulation of the nanocrystalline noble metals which will exhibit an antiproliferative effect in a hyperproliferative skin disorder or disease such as psoriasis when applied to the affected area. A single application of the formulations of the present invention may be sufficient, or the formulations may be applied repeatedly over a period of time, such as several times a day for a period of days or weeks. The amount of the active ingredient, that is the nanocrystalline noble metal in the form of a coating, powder or dissolved in liquid solution, will vary with the conditions being treated, the stage of advancement of the condition, and the type and concentration of the formulation being applied. Appropriate amounts in any given instance will be readily apparent to those skilled in the art or capable of determination by routine experimentation.

"Nanocrystalline" is used herein to denote single-phase or multi-phase polycrystals, the grain size of which is less than about 100, more preferably < 50 and most preferably < 25 nanometers in at least one dimension. The term, as applied to the crystallite or grain size in the crystal lattice of coatings, powders or flakes of the noble metals, is not meant to restrict the particle size of the materials when used in a powder form.

"Powder" is used herein to include particulate sizes of the nanocrystalline noble metals ranging from nanocrystalline powders to flakes.

"Grain size", or "crystallite size" means the size of the largest dimension of the crystals in the noble metal coating or powder.

"Hyperproliferative skin disorders" is used herein to include psoriasis and its varied clinical forms, Reiter's syndrome, pityriasis rubra pilaris, and hyperproliferative variants of the disorders of keratinization.

"Antiproliferative" is used herein to denote effects on the skin including, but not limited to decreasing inflammation, to retarding or normalizing epidermal proliferation and keratinization to produce beneficial effects on hyperproliferative disorders of the skin.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Nanocrystalline forms of the noble metals Ag, Au, Pt, and Pd can be prepared as nanocrystalline powders or coatings, or as solutions prepared by dissolving the nanocrystalline coatings or powders. The nanocrystalline coatings or powders are most preferably prepared with atomic disorder, in accordance with the techniques published in the prior patent applications of Burrell *et al.*, see for example WO 93/23092, published November 25, 1993, WO 95/13704, published May 26, 1995 and WO 98/41095, published

September 24, 1998.

A. Nanocrystalline Noble Metal Coatings on Dressings

Dressings carrying nanocrystalline coatings of noble metals in accordance with the invention include at least one, and preferably at least two or three layers of medical dressing materials, laminated together by known means such as low temperature thermal fusing, stitching or, most preferably, ultrasonic welding. A three layer dressing preferably includes a first layer which will be skin facing in use, a second layer which preferably forms an absorbent core, and a third layer above the second layer. The layers can be laminated together by ultrasonic welds at intermittent locations across the dressing. The first, and preferably the third layer, includes a nanocrystalline coating of one or more of the noble metals.

The dressing may include an occlusive or semi-occlusive layer such as an adhesive tape or polyurethane film in order to secure the dressing in place, and retain moisture for release of ions, atoms, molecules or clusters of the noble metal (hereinafter noble metal species).

The preferred and alternate compositions of the dressing layers, together with the preferred nanocrystalline noble metal coatings, are set out in further detail below.

i) Dressing Materials

The first layer of the dressing is formed of a perforated, preferably non-adherent material which allows for fluids to penetrate or diffuse there through in either or both directions. The perforated material may be formed of a woven or non-woven, non-woven being preferred, fabric such as cotton, gauze, a polymeric net or mesh such as polyethylene, nylon, polypropylene or polyester, an elastomer such as polyurethane or polybutadiene elastomers, or a foam such as open cell polyurethane foam. Exemplary perforated, non-adherent materials useful for the dressing include non-woven meshes such as DELNET™ P530, which is a non-woven veil formed of high density polyethylene using extrusion, embossing and orientation processes, produced by Applied Extrusion Technologies, Inc. Of Middletown, Delaware, USA. This same product is available as Exu-Dry CONFORMANT 2™ Wound Veil, from Frass Survival Systems, Inc., Bronx, New York, USA as a subset of that company's Wound Dressing Roll (Non-Adherent) products. Other useful non-woven meshes include CARELLE™ or NYLON 90™, available from Carolina Formed Fabrics Corp., N-TERFACE™, available from Winfield Laboratories, Inc., of Richardson, Texas,

USA. Exemplary woven meshes may be formed from fibreglass or acetate, or cotton gauze. An exemplary hydrophilic polyurethane foam is HYPOL™, available from W.R. Grace & Co., New York, NY, USA.

For ease of ultrasonic welding for lamination, at least one of the first and second dressing layers is preferably formed from a polymeric material which is amenable to ultrasonic welding, that is which will melt on the application of localized heat and then fuse the layers together on cooling.

The second, absorbent layer is formed from an absorbent material for holding sufficient moisture next to the skin in order to activate the noble metal coating, that is to cause release of ions, molecules, atoms or clusters of the noble metal in order to cause an anti-proliferative effect. Preferably, the absorbent material is an absorbent needle punched non-woven rayon/polyester core such as SONTARA™ 8411, a 70/30 rayon/polyester blend commercially available from Dupont Canada, Mississauga, Ontario, Canada. This product is sold by National Patent Medical as an American White Cross sterile gauze pad. However, other suitable absorbent materials include woven or non-woven materials, non-woven being preferred made from fibers such as rayon, polyester, rayon/polyester, polyester/cotton, cotton and cellulosic fibers. Exemplary are creped cellulose wadding, an air felt of air laid pulp fibers, cotton, gauze, and other well known absorbent materials suitable for medical dressings.

The third layer of the dressing is preferably formed of perforated, non-adherent material such as used in the first layer. This allows moisture penetration as sterile water and the like are added in order to activate the noble metal coating.

Additional layers may be included between or above the first, second and third layers as is well known in medical dressings. Thus the use of the terms first, second and third layer, as used herein and in the claims is not meant to exclude such additional layers.

The first, second and third dressing layers are laminated together at intermittent spaced locations across the dressing by ultrasonic welds. Ultrasonic welding is a known technique in the quilting art. Briefly, heat (generated ultrasonically) and pressure are applied to either side of the dressing at localized spots through an ultrasonic horn so as to cause flowing of at least one of the plastic materials in the first and second layers and the subsequent bonding together of the layers on cooling. The welds appear at localized circular spots and are preferably less than 0.5 cm in diameter. If the third layer is present, the

ultrasonic welding can be performed from either side of the dressing, and will bind all three layers together.

The use of ultrasonic welding of the layers at spaced locations has the advantage of retaining the absorbent and moisture penetration properties of the dressing layers, while retaining the conforming properties of the dressing. Edge seams, stitching, adhesives, or other lamination techniques may be used, but have the disadvantage of interfering with one or more of these desirable properties of the dressings. Furthermore, by spacing the welds at intermittent locations across the dressing, the dressing may be cut to smaller sizes, as needed, without causing delamination. Preferred spacings of about 2.5 cm between welds allows the dressing to be cut down to about 2.5 cm sizes, while maintaining at least one weld to hold the laminated layers together.

ii) Nanocrystalline Coatings of Noble Metals

The dressing preferably includes a nanocrystalline coating of one or more of the noble metals. The coating is applied to one or more of the dressing layers, but is most preferably applied at least to the first and third layers.

The nanocrystalline coating is most preferably formed with atomic disorder in accordance with the procedures set out above and as described in WO 93/23092, WO 95/13704, and WO98/41095, and as set out below. Most preferably, the coating is formed as a multilayer coating of the noble metals, having a top and a base layer, as set below, to produce an interference colour. In this way, the coating provides not only the active ingredient for the treatment of psoriasis, but also acts as an indicator of activation of the dressing. As the top layer of the coating is activated with an alcohol or water-based electrolyte, such as sterile water or ethanol, even minor dissolution of the noble metal results in a detectable colour change, indicating that the coating has been activated. If there is no colour change, additional moisture might be provided to the dressing by adding water, until a colour change is detected. Once activated, the dressing should be maintained in a moist condition, for example by the addition of sterile water, if necessary.

iii) Sterilization

Dressings with nanocrystalline coatings of a noble metal formed with atomic disorder are preferably sterilized without applying excessive thermal energy, which can anneal out the atomic disorder, thereby reducing or eliminating a useful release of noble metal species. Gamma radiation is preferred for sterilizing such dressings, as discussed in WO 95/13704.

Electron beam and ethylene oxide sterilization techniques can also be used.

It should be appreciated that the use of ultrasonic welding to laminate the layers of dressings with nanocrystalline coatings formed from noble metals with atomic disorder is advantageous since it achieves bonding in localized spots and avoids applying heat to any significant portion of the dressing, thereby avoiding any significant reduction in the solubility of the noble metals through annealing out of the atomic disorder.

The sterilized dressings should be sealed in packaging which excludes light penetration to avoid additional oxidation of the noble metal coating. Polyester peelable pouches are preferred. The shelf life of dressings thus sealed is over one year.

iv) Directions for Use of Dressings for Hyperproliferative Skin Disorders and Diseases

The dressing is placed on the affected portion of the skin and is then moistened with drops of sterile water or, for example 70% ethanol, in order to activate the coating for release of noble metal species. The dressing is then secured in place with an occlusive or semi-occlusive layer, such as an adhesive tape or polyurethane film, which keeps the dressing in a moist environment.

As set out in Examples 3 and 4, dressings carrying a bi-layer nanocrystalline noble metal coating formed with silver having atomic disorder, manufactured as set out above and as described in greater detail in Example 1, have shown substantial clinical response in treating psoriasis. In use, the dressings are kept moist, at 100% relative humidity. Adding sterile water initially to activate the noble metal coating is needed, and then as needed to maintain the dressing in a moist condition. Dressings may be changed as required for observation and cleaning, but need not be changed more frequently than every 7 days, and can provide a therapeutic effect for a much longer period of time.

v) Multilayer Nanocrystalline Coatings of Noble Metals With Interference Colour

The dressings preferably include the noble metal coating formed with at least two metal layers, a base layer and a top layer over the base layer, so as to produce an interference colour, as set forth in WO 98/41095. Both layers are partly reflective; the top layer is partly light transmissive. The top layer is a thin film containing at least one noble metal formed with sufficient atomic disorder such that the top layer, in contact with an alcohol or water based electrolyte, releases ions, atoms, molecules or clusters of the noble metal, at a concentration sufficient to provide a therapeutic effect, on a sustainable basis. In this way, the top layer, in contact with the alcohol or electrolyte, will undergo a change in optical path

length, either by a change in thickness resulting from some dissolution, or through a change in the refractive index of the top layer resulting from a change in the composition of a newly formed thin layer formed on the top layer. Either or both of these results are sufficient to cause a detectable colour change, thus providing an indicator that the top layer has been activated.

Both the base layer and the top layer are formed from a partly reflective material. In this way, at least a portion of the incoming light is reflected from the surface of the layer while another portion is transmitted through the layer. The top layer is partly light transmissive to allow incident light to reach the interface with the base layer. The top layer thus cannot approximate 100% reflectivity, such as in pure Al or Ag, or interference colours cannot be generated, as is well known in the art. The materials for the top and base layers should be balanced in their reflectances in order to generate an interference colour. Generally, the top layer is deposited as a thin film having a thickness which maintains adequate transmittance to generate an interference colour. Furthermore, the refractive index for the materials in layers is different, accomplished by differences in their actual or effective compositions. For instance different materials in the two layers will result in the materials having different actual refractive indexes. However, if it is desired to make the layers from the same material, the layers can be deposited with different porosities or different levels/types of atomic disorder, in order to achieve different effective compositions, and thus different refractive indexes.

In this manner, incoming light reflects off the interface of the base and top layers. Incoming light reflects from the interface of the top layer with air, and interferes with the light reflected from the interface with the base layer so as to generate an "interference colour". The particular colour which is generated and its brightness will depend on the properties of the layers, most importantly on the composition of the layers, which determines its transmittance and absorption properties, along with its refractive index, and on the thickness of the layers. Generally, it is desirable to generate first and second order interference colours, by limiting the thickness of the base layer and top layers to minimize the number of internal reflections. First and second order interference colours are generally brighter than third and fourth order etc. colours, making them more aesthetically pleasing, more consistently reproducible in manufacturing, and more susceptible to detectable colour change on variations in thickness on dissolution of even a minor amount of the top layer.

The property which determines the particular colour which is generated is the effective optical thickness of the top layer, that is the product of the refractive index of the top layer material and the actual thickness of the top layer. Thus the colour which is desired can be altered by changing the actual thickness or the top layer or its refractive index.

Preferably, the material in the base layer is a reflective metal. Such metals are known in the art and include, for example one or more of the valve metals; e.g. Ta, Nb, Ti, Zr and Hf, as well as transition metals such as Au, Ag, Pt, Pd, Sn, Cu, V, W and Mo, or the metal Al. More preferably, the base layer is formed from one or more of the noble metals Ag, Au, Pt, and Pd, most preferably Ag, in a partly reflective form.

The base layer may be formed by known techniques, such as the vapour deposition techniques of evaporation or physical vapour deposition. Preferably, the base layer is formed as a thin film by physical vapour deposition with atomic disorder, as set out below and in WO 95/13704, in order to produce a sustainable release of the noble metal species when the base layer is ultimately exposed to an alcohol or water based electrolyte. The thickness of the base layer is generally not critical, provided that it is partly reflective. Preferred thicknesses will vary widely with the material composition. However, in that the layer is preferably a thin film formed by physical vapour deposition techniques, it should be at least about 25 nm thick to create a useful colour. The base layer should be greater than 60 nm thick, more preferably 300 to 2500 nm thick, and most preferably 600 to 900 nm thick.

The top layer is formed of a partly reflective, partly light transmissive thin film containing at least one noble metal, most preferably Ag, formed with atomic disorder so as to produce a sustainable release of the noble metal species, and ultimate colour change, when exposed to an alcohol or a water based electrolyte. The thickness of the top layer formed from these metals is preferably less than 400 nm in order to maintain the preferred level of light transmission. The desired thickness will vary with the composition of the top layer, and with the desired end colour and colour change. For first and second order interference colours, the thickness will generally be less than about 400 nm. More preferably, the thickness will range from 5 to 210 nm, most preferably from 10 to 100 nm.

The top layer may be a thin film of the base layer material, formed with a different refractive index for instance by altering the deposition conditions to change the porosity, composition and/or degree of atomic disorder in the layers.

When the base layer is itself formed from a noble metal with atomic disorder, the top

layer may be provided as an in situ generated top layer by virtue of its thickness and/or composition changing on contacting an alcohol or water based electrolyte, so as to produce an interference colour which differs from the initial colour of the base layer.

Most preferably, the top layer is a thin film of a composite material formed by co-, sequentially or reactively depositing a noble metal in a matrix with atoms or molecules of a different material to create atomic disorder in the matrix, in the manner set out below. The different material is selected from a) biocompatible metals, b) oxygen, nitrogen, hydrogen, boron, sulphur or halogens, or c) an oxide, nitride, carbide, boride, halide, sulphide or hydride of either or both of a noble metal or a biocompatible metal. Most preferably, the top layer material is a composite material containing silver, and one or both of silver oxide and atoms or molecules containing oxygen trapped or absorbed in the silver matrix. The term "silver oxide" is meant to include any oxide or mixture of oxides of silver. However, the top layer is preferably not formed solely of AgO and/or Ag_2O, since the solubility of these materials is low.

vi) Nanocrystalline Coatings of Noble Metals Containing Atomic Disorder

At least the top layer, and preferably also the base layer, is formed in a crystalline form from one or more noble metals with atomic disorder. The production of atomic disorder through physical vapour deposition techniques is described in WO 93/23092 and WO 95/13704, and as outlined below.

The noble metal is deposited as a thin metallic film on one or more surfaces of the dressing by vapour deposition techniques. Physical vapour techniques, which are well known in the art, all deposit the metal from the vapour, generally atom by atom, onto a substrate surface. The techniques include vacuum or arc evaporation, sputtering, magnetron sputtering and ion plating. The deposition is conducted in a manner to create atomic disorder in the coating as defined above. Various conditions responsible for producing atomic disorder are useful. These conditions are generally those which one has been taught to avoid in thin film deposition techniques, since the object of most thin film depositions is to create a defect free, smooth and dense film (see for example J.A. Thornton, "Influence of Apparatus Geometry and Deposition Conditions on the Structure and Topography of Thick Sputtered Coatings," J. Vac. Sci. Technol., 11(4), 666-670, 1974).

The preferred conditions which are used to create atomic disorder during the deposition process include:

- a low substrate temperature, that is maintaining the surface to be coated at a temperature such that the ratio of the substrate temperature to the melting point of the metal (in degrees Kelvin) is less than about 0.5, more preferably less than about 0.35 and most preferably less than about 0.3; and optionally one or both of:

- a higher than normal working (or ambient) gas pressure, i.e. for vacuum evaporation: e-beam or arc evaporation, greater than 0.001 Pa (0.01 mT), gas scattering evaporation (pressure plating) or reactive arc evaporation, greater than 2.67 Pa (20 mT); for sputtering: greater than 10 Pa (75 mT); for magnetron sputtering: greater than about 1.33 Pa (10 mT); and for ion plating: greater than about 26.67 Pa (200 mT); and

- maintaining the angle of incidence of the coating flux on the surface to be coated at less than about 75°, and preferably less than about 30°.

For economic reasons, the thin metal film has a thickness no greater than that needed to provide release of noble metal species on a sustainable basis over a suitable period of time, and to generate the desired interference colour. Within the preferred ranges of thicknesses set out above, the thickness will vary with the particular metal in the coating (which varies the solubility and abrasion resistance), and with the degree of atomic disorder in (and thus the solubility of) the coating. The thickness will be thin enough that the coating does not interfere with the dimensional tolerances or flexibility of the device for its intended utility.

The therapeutic effect of the material so produced is achieved when the coating is brought into contact with an alcohol or a water based electrolyte, thus releasing metal ions, atoms, molecules or clusters. The concentration of the metal species which is needed to produce a therapeutic effect will vary from metal to metal.

The ability to achieve release of metal atoms, ions, molecules or clusters on a sustainable basis from a coating is dictated by a number of factors, including coating characteristics such as composition, structure, solubility and thickness, and the nature of the environment in which the device is used. As the level of atomic disorder is increased, the amount of metal species released per unit time increases. For instance, a silver metal film deposited by magnetron sputtering at $T/Tm < 0.5$ and a working gas pressure of about 0.93 Pa (7 mT) releases approximately 1/3 of the silver ions that a film deposited under similar conditions, but at 4 Pa (30 mT), will release over 10 days. Films that are created with an intermediate structure (ex. lower pressure, lower angle of incidence etc.) have Ag release values intermediate to these values as determined by bioassays. This then provides a method

for producing controlled release metallic coatings. Slow release coatings are prepared such that the degree of disorder is low while fast release coatings are prepared such that the degree of disorder is high.

For continuous, uniform coatings, the time required for total dissolution will be a function of film thickness and the nature of the environment to which they are exposed. The relationship in respect of thickness is approximately linear, i.e. a two fold increase in film thickness will result in about a two fold increase in longevity.

It is also possible to control the metal release from a coating by forming a thin film coating with a modulated structure. For instance, a coating deposited by magnetron sputtering such that the working gas pressure was low (ex. 2 Pa or 15 mT) for 50% of the deposition time and high (ex.4 Pa or 30 mTorr) for the remaining time, has a rapid initial release of metal ions, followed by a longer period of slow release. This type of coating is extremely effective on devices such as urinary catheters for which an initial rapid release is required to achieve immediate anti-microbial concentrations followed by a lower release rate to sustain the concentration of metal ions over a period of weeks.

The substrate temperature used during vapour deposition should not be so low that annealing or recrystallization of the coating takes place as the coating warms to ambient temperatures or the temperatures at which it is to be used (ex. body temperature). This allowable ΔT, that the temperature differential between the substrate temperature during deposition and the ultimate temperature of use, will vary from metal to metal. For the most preferred metal, Ag, preferred substrate temperatures of -20 to 200°C , more preferably -10°C to 100°C are used.

Atomic order may also be achieved, in either or both of the base and top layers by preparing composite metal materials, that is materials which contain one or more noble metals in a metal matrix which includes atoms or molecules different from the noble metals.

The preferred technique for preparing a composite material is to co- or sequentially deposit the noble metal(s) with one or more other inert, biocompatible metals selected from Ta, Ti, Nb, Zn, V, Hf, Mo, Si, Al and alloys of these metals or other metal elements, typically other transition metals. Such inert metals have a different atomic radii from that of the noble metals, which results in atomic disorder during deposition. Alloys of this kind can also serve to reduce atomic diffusion and thus stabilize the disordered structure. Thin film deposition equipment with multiple targets for the placement of each of the noble and biocompatible

metals is preferably utilized. When layers are sequentially deposited the layer(s) of the biocompatible metal(s) should be discontinuous, for example as islands within the noble metal matrix. The final ratio of the noble metal(s) to biocompatible metal(s) should be greater than about 0.2. The most preferable biocompatible metals are Ti, Ta, Zn and Nb. It is also possible to form the anti-microbial coating from oxides, carbides, nitrides, sulphides, borides, halides or hydrides of one or more of the noble metals and/or one or more of the biocompatible metals to achieve the desired atomic disorder.

Another composite material may be formed by reactively co- or sequentially depositing, by physical vapour techniques, a reacted material into the thin film of the noble metal(s). The reacted material is an oxide, nitride, carbide, boride, sulphide, hydride or halide of the noble and/or biocompatible metal, formed in situ by injecting the appropriate reactants, or gases containing same, (ex. air, oxygen, water, nitrogen, hydrogen, boron, sulphur, halogens) into the deposition chamber. Atoms or molecules of these gases may also become absorbed or trapped in the metal film to create atomic disorder. The reactant may be continuously supplied during deposition for codeposition or it may be pulsed to provide for sequential deposition. The final ratio of reaction product to the noble metal(s) should be greater than about 0.05. Air, oxygen, nitrogen and hydrogen are particularly preferred reactants, with oxygen being most preferred.

The above deposition techniques to prepare composite coatings may be used with or without the conditions of lower substrate temperatures, high working gas pressures and low angles of incidence previously discussed. One or more of these conditions are preferred to retain and enhance the amount of atomic disorder created in the coating.

B. Nanocrystalline Powders of Noble Metals

Nanocrystalline powders (i.e., powders formed from particulates having nanocrystalline grain size) of one or more noble metals are most preferably prepared with atomic disorder by the procedures set out in WO 93/23092 and WO 95/13704, or as otherwise known in the art. The powders may be prepared as pure metals, metal alloys or compounds such as metal oxides or metal salts, by vapour deposition, mechanical working, or compressing in order to impart atomic disorder, as set out below, and as in the above-mentioned patent application. Mechanically imparted disorder is conducted by milling, grinding, hammering, mortar and pestle or compressing, under conditions of low temperature (i.e., temperatures less than the temperature of recrystallization of the material) to ensure that

annealing or recrystallization does not take place. Alternatively, nanocrystalline powders may be prepared by preparing nanocrystalline coatings by physical vapour deposition to include atomic disorder in the manner set out above, onto a substrate such as a cold finger or a silicon wafer (or larger substrates), and then scraping off the coating to form a powder. A still further alternative method of powder preparation is to prepare nanocrystalline coatings, such as by physical vapour deposition to include atomic disorder as set out above, onto powdered substrates which are biocompatible. Particularly preferred substrates are bioabsorbable and/or hygroscopic powders such as chitin. Exemplary bioabsorbable and/or hygroscopic powders are composed of :

Synthetic Bioabsorbable Polymers: for example polyesters/polyactones such as polymers of polyglycolic acid, glycolide, lactic acid, lactide, dioxanone, trimethylene carbonate etc., polyanhydrides, polyesteramides, polyortheoesters, polyphosphazenes, and copolymers of these and related polymers or monomers.

Naturally Derived Polymers:

Proteins: albumin, fibrin, collagen, elastin;

Polysaccharides: chitosan, alginates, hyaluronic acid; and

Biosynthetic Polyesters: 3-hydroxybutyrate polymers.

Most preferably, powders of the present invention are sized at less than 100 μm, and more preferably less than 40 μm.

The prepared nanocrystalline powders may then be incorporated into or onto medical dressings or pharmaceutical formulations, by methods known in the art. For example, the powders may be layered onto the substrates (dressings or powders), mechanically mixed within the fibers of the dressings, impregnated into dressings by, for example, physical blowing, or added to topical pharmaceutically acceptable composition ingredients.

The antiproliferative effects of the nanocrystalline powder is achieved when the powder is brought into contact with an alcohol or a water-based electrolyte, thus releasing the noble metal ions, atoms, molecules or clusters.

Nanocrystalline powders may be sterilized as described above, or may be prepared as preserved materials with known preservatives such as methyl paraben or propyl paraben. Alternatively, given the anti-microbial activity of the nanocrystalline powders themselves, they may be considered as being in a preserved form without the addition of preservatives.

C. Formulations and Dosages

Typically, the nanocrystalline noble metals will be formulated from the active ingredient, namely nanocrystalline powders or coatings of the noble metals, or dissolved species from such powders or coatings, in the form of:

- coatings on medical dressings or biocompatible powdered substrates,
- powders included in medical dressings,
- topical pharmaceutical compositions such as gels, pastes, ointments, creams, lotions, emulsions, suspensions or powders,
- liquid pharmaceutical compositions prepared by dissolving nanocrystalline coatings or powders of the noble metals in pharmaceutically acceptable carriers such as water, for application in drop, mist or aerosol forms.

In the pharmaceutical compositions, the amount of the nanocrystalline metal powder may range broadly from about 0.001% to about 30% by weight, but will more preferably fall in the range of from about 0.01 to 5% by weight. Coatings of the nanocrystalline noble metals may be very thin, or thicker, depending on the desired duration of application on the patient. Typical coating thicknesses are in the range of 150 to 3000 nm thick. As liquid formulations, the amount of dissolved noble metal will typically range between about 0.001 to 1% by weight.

Nanocrystalline gels may be formed from the nanocrystalline metal powder in admixture with gelling agents such as carboxymethyl cellulose (CMC), polyvinyl alcohol (PVA), collagen, pectin, gelatin, agarose, chitin, chitosan, and alginate, with the gelling agent comprising between about 0.01 - 20 % w/v.

Besides the active ingredient, pharmaceutical compositions may also include non-toxic, pharmaceutically and dermatologically acceptable carriers, diluents and excipients, suitable for topical application, as are well known, see for example Merck Index, Merck & Co., Rahway, N.J., Bioreversible Carriers in Drug Design, Theory and Application, Roche (ed.) Pergamon Press, (1987), Gilman et al., (eds) (1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; Novel Drug Delivery Systems, 2nd Ed., Norris (ed.) Marcel Dekker Inc., (1989), and Remington's Pharmaceutical Sciences. For standard dosages of conventional pharmacological agents, see, e.g., Physicians Desk Reference (1997 Edition); and American Medical Association (1997) Drug Evaluations (Subscriptions).

Dosage forms for the topical administration of compositions of the nanocrystalline noble metals include various mixtures and combinations that can be applied topically and will permit even spreading and absorption into the cutaneous surfaces. Examples include sprays, mists, aerosols, lotions, creams, solutions, gels, ointments, pastes, emulsions, and suspensions. The active compound can be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required. Topical preparations can be prepared by combining the noble metal powder with conventional pharmaceutically acceptable diluents and carriers commonly used in topical dry, liquid, cream and aerosol formulations. Ointment and creams can, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. An exemplary base is water. Thickening agents which can be used according to the nature of the base include aluminum stearate, hydrogenated lanolin, and the like. Lotions can be formulated with an aqueous or oily base and will, in general, also include one or more of the following: stabilizing agents, emulsifying agents, dispersing agents, suspending agents, thickening agents, coloring agents, perfumes, and the like. Powders can be formed with the aid of any suitable powder base, e.g., talc, lactose starch and the like. Drops can be formulated with an aqueous base or non-aqueous base, and can also include one or more dispersing agents, suspending agents, solubilizing agents, and the like.

Ointments, pastes, creams and gels also can contain excipients, such as starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, and talc, or mixtures thereof. Powders and sprays also can contain excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Solutions of nanocrystalline noble metals can be converted into aerosols or sprays by any of the known means routinely used for making aerosol pharmaceuticals. In general, such methods comprise pressurizing or providing a means for pressurizing a container of the solution, usually with an inert carrier gas, and passing the pressurized gas through a small orifice. Sprays can additionally contain customary propellants, such a chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Multiple inactive ingredients are generally incorporated in topical formulations to improve cosmetic acceptability, and are optional ingredients in the formulations. Examples of ingredients are emulsifiers, thickening agents, solvents, anti-foaming agents, preservatives,

fragrances, coloring agents, emollients, and fillers.

Materials to avoid in formulations of the present invention in amounts greater than 0.01 % w/v. include chloride salts, aldehydes, ketones, long chain alcohols (with the exception of polyvinyl alcohols, preferably no greater than C_8-alcohols, and preferably no greater than C_6-alcohols), glycerol, and triethanolamine.

The dosage of the active ingredients depends upon many factors that are well known to those skilled in the art, for example, the particular form of the active ingredient, the condition being treated, the age, weight, and clinical condition of the recipient patient, and the experience and judgement of the clinician or practitioner administering the therapy. A therapeutically effective amount of the nanocrystalline noble metal is that which provides either subjective relief of symptoms or an objectively identifiable improvement as noted by the clinician or other qualified observer. The dosing range varies with the metal used, its form, the route of administration and the potency of the particular compound.

D. Methods of Treating Hyperproliferative Skin Disorders and Diseases

The invention provides methods of treating hyperproliferative skin disorders and diseases such as psoriasis, by administering a therapeutically effective amount of a nanocrystalline noble metal powder, or a solution derived from a nanocrystalline noble metal, as either a topical formulation, or as a coating on medical dressing, applied to the locally affected diseased or abnormal skin area. A therapeutically effective amount may be determined by applying formulations containing the nanocrystalline noble metals to test animal models. Topical applications may be applied one or more times a day. Dressings coated with the nanocrystalline noble metals may be changed daily, or even less frequently, and should be kept in a moist condition with the addition of saline, alcohols, or more preferably sterile water, in order to release ions, atoms, molecules or clusters of the nanocrystalline metal, on a sustained basis.

E. Examples

Example 1 - Preparation of Nanocrystalline Silver Coatings on Dressings

This example shows the preparation of a bilayer nanocrystalline silver coating on a dressing material. A high density polyethylene dressing, DELNET™ or CONFORMANT 2™ was coated with a silver base layer and a silver/oxide top layer to generate a coloured anti-microbial coating having indicator value. The coating layers were formed by magnetron sputtering under the conditions set out in Table 1.

Table 1

Sputtering Conditions:	Base Layer	Top Layer
Target	99.99% Ag	99.99% Ag
Target Size	20.3 cm diameter	20.3 cm diameter
Working Gas	96/4 wt% Ar/O_2	96/4 wt% Ar/O_2
Working Gas Pressure	5.33 Pa (40 mT)	5.33 Pa (40 mT)
Power	0.3 kW	0.15 kW
Substrate Temperature	20°C	20°C
Base Pressure	3.0 X 10^{-6} Torr	3.0 X 10^{-6} Torr
Anode/Cathode Distance	100 mm	100 mm
Sputtering Time	7.5 - 9 min	1.5 min
Voltage	369 - 373 V	346 V

The resulting coating was blue in appearance. A fingertip touch was sufficient to cause a colour change to yellow. The base layer was about 900 nm thick, while the top layer was 100 nm thick.

To establish that silver species were released from the coated dressings, a zone of inhibition test was conducted. Mueller Hinton agar was dispensed into Petri dishes. The agar plates were allowed to surface dry prior to being inoculated with a lawn of *Staphylococcus aureus* ATCC#25923. The inoculant was prepared from Bactrol Discs (Difco, M.), which were reconstituted as per the manufacturer's directions. Immediately after inoculation, the coated materials to be tested were placed on the surface of the agar. The dishes were incubated for 24 hr. at 37°C. After this incubation period, the zone of inhibition was calculated (corrected zone of inhibition = zone of inhibition - diameter of the test material in contact with the agar). The results showed a corrected ZOI of about 10 mm, demonstrating good release of silver species.

The coating was analyzed by nitric acid digestion and atomic absorption analysis to contain 0.24 +/- 0.04 mg silver per mg high density polyethylene. The coating was a binary alloy of silver (>97%) and oxygen with negligible contaminants, based on secondary ion mass spectroscopy. The coating, as viewed by SEM, was highly porous and consisted of equiaxed nanocrystals organized into coarse columnar structures with an average grain size of 10 nm. Silver release studies in water demonstrated that silver was released continuously from the coating until an equilibrium concentration of about 66 mg/L was reached (determined by atomic absorption), a level that is 50 to 100 times higher than is expected from bulk silver metal (solubility ≤ 1mg/L).

By varying the coating conditions for the top layer to lengthen the sputtering time to 2

min, 15 sec., a yellow coating was produced. The top layer had a thickness of about 140 nm and went through a colour change to purple with a fingertip touch. Similarly, a purple coating was produced by shortening the sputtering time to 1 min, to achieve a top layer thickness of about 65 nm. A fingertip touch caused a colour change to yellow.

To form a three layer dressing, two layers of this coated dressing material were placed above and below an absorbent core material formed from needle punched rayon/polyester (SONTARA™ 8411). With the silver coating on both the first and third layers, the dressing may be used with either the blue coating side or the silver side in the skin facing position. For indicator value, it might be preferable to have the blue coating visible. The three layers were laminated together by ultasonic welding to produce welds between all three layers spaced at about 2.5 cm intervals across the dressing. This allowed the dressing to be cut down to about 2.5 cm size portions for smaller dressing needs while still providing at least one weld in the dressing portion.

The coated dressings were sterilized using gamma radiation and a sterilization dose of 25 kGy. The finished dressing was packaged individually in sealed polyester peelable pouches, and has shown a shelf life greater than 1 year in this form. The coated dressings can be cut in ready to use sizes, such as 5.1 x 10.2 cm strips, and slits formed therein before packaging. Alternatively, the dressings may be packaged with instructions for the clinician to cut the dressing to size and form the desired length of the slit for the medical device.

Additional silver coated dressings were prepared in a full scale roll coater under conditions to provide coatings having the same properties set out above, as follows:

- the dressing material included a first layer of silver coated DELNET, as set out above, laminated to STRATEX, AET, 8.0NP$_2$-A/QW, which is a layer of 100% rayon on a polyurethane film.
- Silver Foam Dressing - three layers of silver coated high density polyethylene prepared as above, alternating with two layers of polyurethane foam, L-00562-6 Medical Foam, available from Rynel Ltd., Bootbay, Maine, USA.

Example 2 - Preparation of Nanocrystalline Silver Powders

Nanocrystalline silver powder was prepared by preparing silver coatings on silicon wafers, under the conditions set forth in Table 1, and then scraping the coating off using a glass blade.

Nanocrystalline silver powder was also prepared by sputtering silver coatings on

silicon wafers using Westaim Biomedical NGRC unit, and then scraping the coating off. The sputtering conditions were as follows:

Table 2 - Sputtering Conditions

Target:	99.99% Ag
Target Size:	15.24 cm X 1216.125 cm
Working Gas:	75:25 wt% Ar/O_2
Working Gas Pressure:	40 mTorr
Total Current:	40 A
Base Pressure:	$5.0 X10^{-5}$ Torr
Sandvik Belt Speed:	340 mm/min
Voltage:	370 V

The powder has a particle size ranging from 2 μm to 100 μm, with crystallite size of 8 to 10 nm, and demonstrated a positive rest potential.

Example 3 - Treatment of Psoriasis

This patient was a 58 year old female with psoriatic plaques covering up to sixty percent of her body. For this patient, psoriatic plaques first occurred ten years ago and have been treated with the following:

1. Adrenal corticosteroids. Injections gave relief from pruritus and general discomfort. Treatments led to a rebound effect; i.e. psoriasis would flare up after treatments wore off. Corticosteroids were discontinued.
2. UV Light and Methotrexate treatments. UV light treatments were given in conjunction with methotrexate. The UV light treatments caused burns and new lesions. The methotrexate caused severe nausea. Both treatments were discontinued.
3. Ice Cap Spray. This treatment contained a potent corticosteroid, and gave some relief but it was taken off the market and is no longer available.
4. Soriatone (acetretin 10 mg). This systemic retinoid treatment was associated with joint aches and was discontinued.
5. Diet. The patient was attempting to control the disease through diet.

Nanocrystalline silver was tested as follows. Nanocrystalline silver was deposited on sheets of high-density polyethylene (HDPE) using a vapour deposition process as set forth in Example 1. Two sheets of this coated HDPE were laminated together around a core of non-woven rayon polyester, as set forth in Example 1. A 50 mm X 50 mm (2" X 2") piece of this composite material was saturated with water and placed centrally on a one and a half year old 150 mm X 100 mm (6" X 4") psoriatic plaque on the patient's flank. The nanocrystalline

silver coated material was covered with a piece of low moisture vapour transmission thin polymer film. The polymer sheet extended 50 mm (2") beyond the nanocrystalline silver coated HDPE to provide control data regarding occlusion of the psoriatic plaque.

The dressing was removed after three days. There was no discernible change in the plaque at this time. However two days later the area that was covered with the nanocrystalline silver had the appearance of normal skin while the rest of the plaque was still rough and unchanged, including the untreated but occluded area.

The nanocrystalline silver therapy caused the treated psoriatic plaque to resolve.

Example 4 - Treatment of Psoriasis

This patient was a 58 year old female with psoriatic plaques over up to sixty percent of her body. Psoriatic plaques had first occurred ten years ago and had been treated with the following:

1. Adrenal corticosteroids. Injections gave relief from pruritus and general discomfort. Treatments led to a rebound effect i.e. psoriasis would flare up after treatments wore off. Corticosteroids were discontinued.
2. UV Light and Methotrexate treatments. UV light treatments were given in conjunction with methotrexate. The UV light treatments caused burns and new lesions. The methotrexate caused severe nausea. Both treatments were discontinued.
3. Ice Cap Spray. This treatment contained a potent corticosteroid, and gave some relief but it was taken off the market and is no longer available.
4. Soriatone (acetretin 10 mg). This systemic retinoid treatment was associated with joint aches and was discontinued.
5. Diet. The patient was attempting to control the disease through diet.

Nanocrystalline silver was tested as follows. Nanocrystalline silver was deposited on sheets of high-density polyethylene (HDPE) using a vapour deposition process as set forth in Example 1 (top layer). Two sheets of this coated HDPE were laminated together around a core of non-woven rayon polyester, as set forth in Example 1. A 50 mm X 50 mm (2" X 2") piece of this composite material was saturated with water and placed centrally on a 125 mm X 100 mm (5" X 4") psoriatic plaque on the patient's upper left thigh. The nanocrystalline silver coated material was covered with a piece of low moisture vapour transmission thin polymer film. The polymer sheet extended 50 mm (2") beyond the nanocrystalline silver coated HDPE to provide control data regarding occlusion of the psoriatic plaque.

The dressing was removed and the plaque examined after two days. The area that was covered with the nanocrystalline silver was free of scaling and only slightly erythenatous while the rest of the plaque was still erythenatous and scaly, including the untreated but occluded area. The plaque was redressed with a similar 50 mm X 50 mm (2" X 2") piece of nanocrystalline silver coated dressing, which was left in place for a further period of 2 days. The area that was covered with the nanocrystalline silver remained free of scale and only slightly erythenatous, while the rest of the plaque was still erythenatous and scaly, including the area under the occlusive film.

The nanocrystalline silver therapy caused the treated psoriatic plaque to resolve.

Example 5 - Preparation of Nanocrystalline Gels

A commercial carboxymethyl cellulose/pectin (Duoderm Convatec™) was combined with nanocrystalline silver powder prepared as in Example 2 to produce a gel with 0.1% w/v. silver. Carboxymethyl cellulose (CMC) fibers were coated by magnetron sputtering, under conditions similar to those set out in Example 1 for the top layer to produce a defective nanocrystalline silver coating. The CMC was then gelled in water by adding 2.9 g to 100 mL volume. An alginate fibrous substrate was directly coated with a defective nanocrystalline silver coating by magnetron sputtering under coating conditions similar to those set forth in Example 1 for the top layer. The alginate (5.7 g) was added to 100 mL volume of water to create a gel. A commercial gel containing CMC and alginate (Purilon gel Coloplast™) was mixed with an atomic disordered nanocrystalline silver powder prepared as in Example 2 to give a gel product with 0.1 % w/v silver. A commercially available gel (Lubriderm™ - glyceryl polymethacrylate) was blended with atomic disordered nanocrystalline silver powder prepared as in Example 2, to prepare a gel with a silver content of 0.1 % w/v. A further gel was formulated with, on w/v basis, 0.1 % methyl paraben, 0.02 % propyl paraben, 0.5% polyvinyl alcohol (Airvol™ PVA 540), 2% CMC, 0.1 % nanocrystalline silver powder prepared as in Example 2, and was then brought up to 1000 g with water.

All publications mentioned in this specification are indicative of the level of skill in the art of this invention. All publications are herein incorporated by reference to the same extent as if each publication was specifically and individually indicated to be incorporated by reference.

The terms and expressions used are, unless otherwise defined herein, used as terms of description and not limitation. There is no intention, in using such terms and expressions, of

excluding equivalents of the features illustrated and described, it being recognized that the scope of the invention is defined and limited only by the following claims.

We claim:

1. The use of one or more noble metals in a nanocrystalline form, for the treatment of a hyperproliferative skin disorder.

2. The use as set forth in claim 1, wherein the one or more noble metals are characterized by sufficient atomic disorder, such that the metal, in contact with an alcohol or water-based electrolyte, releases atoms, ions, molecules, or clusters of at least one noble metal on a sustainable basis.

3. The use as set forth in claim 2, wherein the one or more noble metals is nanocrystalline silver, and wherein the hyperproliferative skin disorder is psoriasis.

4. The use as set forth in claim 1, wherein the one or more noble metals are provided as a coating on, or filler in, a dressing, or in a pharmaceutical composition with one or more pharmaceutically and dermatologically acceptable carriers, diluents, or excipients suitable for topical application.

5. The use as set forth in claim 4, wherein the pharmaceutical composition includes a nanocrystalline powder of the one or more noble metals, or a solution containing dissolved species from a nanocrystalline powder or coating of the one or more noble metals.

6. The use as set forth in claim 5, wherein the pharmaceutical composition is a gel, cream or lotion containing the nanocrystalline powder of the one or more noble metals in an amount of 0.01 - 5 % by weight, or a liquid containing 0.001 - 1 % by weight of the one or more noble metals.

7. The use as set forth in claim 6, wherein the hyperproliferative skin disorder is psoriasis, and wherein the one or more noble metals is nanocrystalline silver formed with sufficient atomic disorder such that, in contact with an alcohol or water based electrolyte, the silver releases ions, atoms, molecules or clusters of the silver on a sustainable basis.

8. The use as set forth in claim 4, wherein the coating is provided on a dressing.

9. The use as set forth in claim 8, wherein the coating is 150 - 3000 nm thick.

10. The use as set forth in claim 8, wherein the nanocrystalline noble metal coating comprises:

a base layer of a partly reflective material capable of generating an interference colour when covered with a partly reflective, partly light transmissive top layer;

a top layer formed over said base layer, said top layer being a partly reflective, partly light transmissive thin film containing at least one noble metal and having a thickness such

that a first or second order interference colour is produced, said top layer having a refractive index different from that of the base layer, and the noble metal being formed with sufficient atomic disorder such that the top layer, in contact with an alcohol or water based electrolyte, releases ions, atoms, molecules or clusters of the noble metal into the alcohol or water based electrolyte on a sustainable basis.

11. The use as set forth in claim 10, wherein the dressing fixed in place with an occlusive or semi-occlusive layer which maintains the dressing in a moist condition.

12. The use as set forth in claim 11, wherein the occlusive or semi-occlusive layer is an adhesive tape or film.

13. A pharmaceutical composition in topical administration form which comprises a therapeutically effective amount of one or more noble metals in a nanocrystalline form, in admixture with one or more pharmaceutically and dermatologically acceptable carriers, diluents, or excipients suitable for topical application.

14. The pharmaceutical composition as set forth in claim 13, wherein the one or more noble metals is provided as a nanocrystalline powder of the one or more noble metals, or as a solution containing dissolved species from a nanocrystalline powder or coating of the one or more noble metals.

15. The pharmaceutical composition as set forth in claim 14, formulated as a gel, cream or lotion containing the nanocrystalline powder of the one or more noble metals in an amount of 0.01 - 5 % by weight, or as a liquid containing 0.001 - 1 % by weight of the one or more noble metals.

16. The pharmaceutical composition as set forth in claim 15, for use in the treatment of psoriasis, and wherein the one or more noble metals is nanocrystalline silver formed with sufficient atomic disorder such that, in contact with an alcohol or water based electrolyte, the silver releases ions, atoms, molecules or clusters of the silver on a sustainable basis.